Modelling the effects of propofol on neuronal synchronization in network of interneurons

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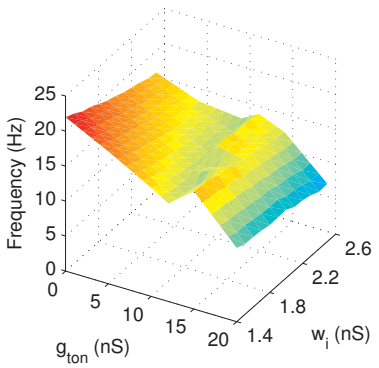
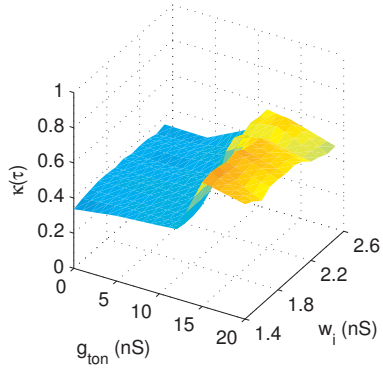
Propofol is a chemical agent commonly used as an intravenous general anesthetic. At the cellular level, this short-acting ananesthetic positively modulates GABAergic inhibitory activity by targeting GABA-A receptors [1]. This type of receptors are widespread in the brain and can be present both within synaptic clefts, as well as on extrasynaptic locations along the dendrites and neuron membrane where they are responsible for tonic inhibition. At the macroscopic level of SEEG (deep Stereographic-Electro Encephalogram) or EEG (Electro Encephalogram) recordings, one observes, with certain doses of propofol, a paradoxical excitation phenomenon [2] the generation mechanisms of which are not clearly understood. In this study, we suggest a potential mechanism for the appearance of paradoxical excitation occurring under propofol-induced general anaesthesia.

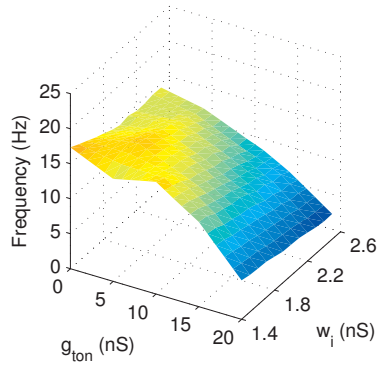
We show, with a model network of Hodgkin-Huxley neurons, that tonic inhibition – induced by the binding of propofol to extra-synaptic receptors – together with an increase of the synaptic time constant within an certain range [3] can account for the phenomenon of paradoxical excitation. However, changes in the gain (or conductance) of the synaptic inhibition do not correspond to a sudden increase in neuronal population firing rate nor synchrony as described in the experiments [3]. The action of propofol on extrasynaptic GABAergic receptors was modelled by varying the conductance g_{ton} of a tonic current in the form $I_{ton} = g_{ton}(V - E_{ton})$ as described in [4]. Figure 1 shows the evolution of the neuronal population firing rate and the coherence (or synchrony) of the network activity as the tonic inhibition and the synaptic conductance vary. The plots are given for different values of the synaptic time constants. The increase of these three variables, synaptic time constant and conductance, and tonic conductance reflect an increase in propofol doses.



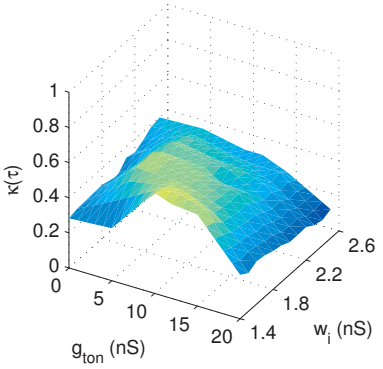
(a) Network frequency for $\tau_i = 10\,ms$.



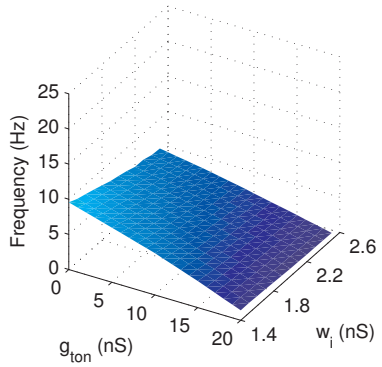
(b) Network synchronisation for $\tau_i = 10\,ms$.



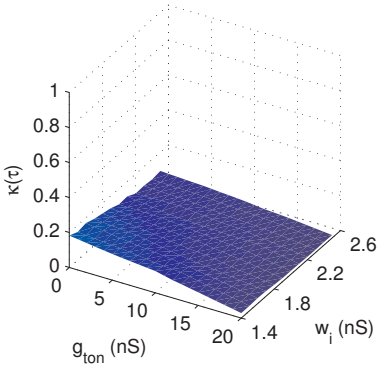
(c) Network frequency for $\tau_i = 14\,ms$.



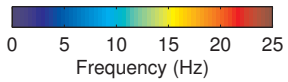
(d) Network synchronisation for $\tau_i = 14\,ms$.



(e) Network frequency for $\tau_i = 30\,ms$.



(f) Network synchronisation for $\tau_i = 30\,ms$.



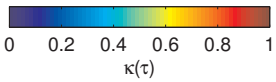


Figure 1: Propofol-enhanced tonic inhibition allows for tighter network synchronisation, regardless of the presence of stronger inhibitory synapses. In all the plots, the x axis represents the tonic conductance (g_{ton}) and the y axis represents the inhibitory synaptic weight (w_i). (A) Given $\tau_i = 10\,ms$, the network frequency decelerates as tonic inhibition strengthens until a critical value at which it accelerates. (B) This acceleration is due to an abrupt increase in network synchronisation at $g_{ton} \geq 15\,nS$ for all values of w_i. (C) A longer synaptic time constant ($\tau_i = 14\,ms$) shifts the network frequency bump towards lower values of g_{ton}. (D) Similarly, the network synchronisation bump shifts towards lower values of g_{ton}. (E) Extending the synaptic time constant ($\tau_i = 30\,ms$) causes the bump-like pattern of the network frequency to disappear in favour of a linearly decelerating trend. (F) Similarly, the bump-like pattern of the network synchronisation disappears in favour of a linearly decelerating trend. The network was stimulated with a constant current $I_{stim} = 0.4\,nA$.

Acknowledgements

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